REMARKS

Claims 38, 39, 44-51, 53, 60, 73-76, and 81 are pending in the application and have been examined. Claims 40-43, 56-59, and 77-80 are withdrawn as being directed to non-elected subject matter. Claims 38, 39, 44-51, 53, 60, 73-76, and 81 stand rejected. Claims 38, 53, 57, 58, and 73 have been amended. Claims 82 and 83 have been added. No new matter has been introduced. Reconsideration and allowance of Claims 38, 39, 44-51, 53, 60, 73-76, and 81-83 is respectfully requested.

The Rejection of Claims 38, 39, 44-51, 53, 73-76, and 81 Under 35 U.S.C. § 103(a) as Being Unpatentable Over U.S. Patent No. 5,972,880 (Pelletier et al.) in View of U.S. Patent No. 5,206,023 (Hunziker)

Claims 38, 39, 44-51, 53, 73-76, and 81 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,972,880 (Pelletier et al.) in view of U.S. Patent No. 5,206,023 (Hunziker). The Examiner has taken the position that Pelletier et al. discloses the intra-articular injection of a catabolic inhibitor, IL-1ra, for the treatment of osteoarthritis. The Examiner further characterizes Pelletier et al. as establishing a connection between the biological effects of IL-1 and those of transforming growth factor beta, wherein the IL-1 has been shown to modulate the effect of TGF beta on the body (with reference to Col. 4, lines 1-20). The Examiner admits that Pelletier et al. does not disclose administering a composition comprising anabolic promoting compounds such as TGF-beta. The Examiner cites Hunziker as disclosing the administration of growth factors to cartilage defects, and concludes that because the cited references each disclose compositions for the treatment of cartilage damage, it would be within the level of skill in the art to combine them in order to provide an improved cartilage treatment composition.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Applicants disagree with the Examiner's conclusion and respectfully traverse this ground of rejection.

While not acquiescing to the Examiner's position, but in order to facilitate prosecution, Claim 38, from which Claims 39, 44-51, and 53 depend, and Claim 73, from which Claims 74-76 and 81 depend have been amended to remove certain classes of chondroprotective agents. Applicants maintain the right to pursue the subject matter removed from Claims 38 and 73 in one or more continuation applications.

It is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness because there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or combine the referenced teachings as proposed by the Examiner. Rather, the cited references teach directly away from the claimed invention, as discussed below.

Obviousness is determined by analyzing the factual inquires set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ459 (1966). The inquiry under Graham includes ascertaining the differences between the prior art and the claims at issue.

The differences between Pelletier et al. and Claims 38 and 73

Claim 38 and 73 are directed to method of inhibiting cartilage degradation in a joint of a patient comprising delivering to the joint a composition in solution comprising a therapeutically effective amount of *an anabolic chondroprotective agent* and a therapeutically effective amount of *an inhibitor of cartilage catabolism.*

It is the position of the Examiner that Pelletier et al. teaches a method of treating osteoarthritis comprising the intra-articular administration of compounds that inhibit cartilage catabolism, such as interleukin receptor antagonists. The Examiner admits that Pelletier et al. does not teach administering a composition comprising anabolic promoting compounds, such as

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

TGF-beta. As described below, it is noted that Pelletier et al. teaches directly away from the administration of TGF-beta. Pelletier et al. also does not teach or remotely suggest administering a composition comprising a combination of compounds that inhibit cartilage catabolism and compounds that promote cartilage anabolic processes, as claimed.

The differences between Hunziker and Claims 38 and 73

The Examiner has taken the position that Hunziker teaches methods for treatment and repair of defects of lesions in cartilage comprising injection of a composition comprising anabolic promoting compounds such as TGF-beta. The Examiner admits that Hunziker does not teach administering a composition comprising a compound that inhibits cartilage catabolism. Nor does Hunziker teach or remotely suggest administering a composition comprising a combination of compounds that inhibit cartilage catabolism and compounds that promote cartilage anabolic processes, as claimed.

The Combined Teachings of Pelletier et al. and Hunziker

As acknowledged by the Examiner, Pelletier et al. does not teach administering a composition comprising anabolic promoting compounds, such as TGF-beta. Further in this regard, it is noted that Pelletier et al. teaches directly away from administering TGF-beta to a joint.

Pelletier et al. is generally directed to the use of rhIL-1ra to reduce the osteophyte formation and severity of cartilage lesions in osteoarthritis. Pelletier et al. teaches that together with cartilage degeneracy, osteophytes (small abnormal body outgrowths) occur and develop on the stripped part of the articular bones (first column). A canine ACL model of osteoarthritis was used to examine the action of intraarticular injections of rhIL-1ra on cartilage lesions and the presence of osteophyte formation. As stated in Pelletier et al., "The degree of osteophyte formation was graded by measuring the maxmal width (mm) of the spur on each femoral

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

condyle." Col. 5, lines 17-20. As further stated in Pelletier et al., "Dogs treated with rhIL-1ra presented a dose-dependent *decrease* in the incidence and size of osteophytes on condyles." Col. 8, lines 1-3.

With regard to the mechanism responsible for the rhIL-1ra induced decrease in osteophytes, Pelletier et al. states that "it is conceivable that the increase in the local synthesis of growth factors or proinflammatory cytokines by the inflamed synovium may be an important factor in osteophyte formation." Col. 4, lines 17-20. In particular, Pelletier et al. states, "inhibition of IL-1 effect would decrease cell mitosis rate and hence modulate the action of TGF-beta by *reducing the biological effect* of this growth factor." Col. 4, lines 13-16 (emphasis added). In further support of the concept that increased local levels of TGF-beta may induce osteophyte formation, Pelletier et al. notes, "Injections of TGF-beta in the murine knee joint induces the outgrowth of chondroid tissue at the femoral ridges." Col. 4, lines 11-13. Therefore, Pelletier et al. teaches the desirability of *reducing articular levels of TGF-beta* in order to reduce osteophyte formation, and thus teaches directly away from the administration of TGF-beta in combination with IL-1Ra.

The Examiner admits that Pelletier et al. teaches "inhibiting IL-1 effects *decrease* tissue growth and the effects of TGF-beta." However, the Examiner asserts that Pelletier et al. does not teach away from the use of growth factors, "only suggesting that excessive growth factors might play a role in osteophytes formation, suggesting that modulation would be in order." Applicants strongly disagree with the Examiner's conclusion that Pelletier et al. does not teach away from the claimed invention. Indeed, the very mechanism proposed in Pelletier for the efficacy of the administration of rIL-1ra is the *reduction of the biological effect of TGF-beta,* thereby reducing osteophyte formation. Therefore, in view of this teaching of Pelletier, one of skill in the art would certainly not be motivated to administer the combination of rIL-1ra and TGF-beta made

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

by the Examiner, because Pelletier et al. teaches that such a combination would not be expected to be effective.

As stated in M.P.E.P. § 2143.01, "[T]he test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts." In determining whether an invention is obvious, it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Telflex Inc.*, 127 S.Ct. 1727, 1731, (2007). "Where the teaching of a reference discourages research in field where applicants made their invention and thus, applicants invented a method for producing a product in the face of art strongly suggesting that such method would produce unacceptable results, this is antithesis of obviousness." *In re Rosenberger*, 386 F.2d 1015 (1967).

Therefore, it is demonstrated that in view of the teachings of Pelletier et al., one of skill in the art would not have any motivation or expectation of success to administer a composition comprising a combination of rhIL-1ra and TGF-beta to a joint, as claimed. Hunziker does not cure the deficiencies of Pelletier et al. because Hunziker does not teach or suggest the use of a combination of compounds that inhibit cartilage catabolism and compounds that promote cartilage anabolic processes, as claimed.

Unexpected Results and Substantial Advantages

Further, nothing in the prior art of record even remotely addresses an unexpected result obtained by the claimed invention, namely that inhibitors of cartilage catabolism, when administered together with an anabolic chondroprotective agent, have the potential to not only inhibit inflammation and matrix degradation, but to also restore the ability of the diseased chondrocytes to respond to anabolic growth factors, and thus permit repair of the damaged

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

cartilage, as documented in the specification and verified by experimental data. It is noted that applicants have submitted an extensive collection of data during the prosecution of the present application, demonstrating the advantages and unexpected results of the present invention, which has not been considered by the Examiner in the context of the claimed invention, as amended. To ensure due consideration, applicants briefly reprise experimental data establishing unexpected results from the present invention established in (1) non-prior art references (publications by Studer et al.) that were submitted with the response filed by applicants on January 3, 2006, and (2) additional experimental data that was submitted with the response filed by applicants on November 6, 2006.

(1) On January 3, 2006, applicants previously submitted non-prior art reference Studer et al., *J. Orthopaedic Research 21*:914-921 (2003) which demonstrated that the combination of IGF-1 (an anabolic chondroprotective agent) and the iNOS inhibitor L-NMA (an inhibitor of cartilage catabolism) stimulated proteoglycan synthesis in diseased chondrocytes while the individual agents had little to no effect on their own. Previously submitted non-prior art reference Studer et al., *J Orthopaedic Research 23*:454-461, 2005) further demonstrated that TGF-beta (an anabolic chondroprotective agent) and the COX-2 inhibitor SC-58125 (an inhibitor of cartilage catabolism) stimulated proteoglycan synthesis in diseased chondrocytes while the individual agents had little to no effect on their own. In addition, Studer (2005) examined the effect of various combinations on the expression of TIMP-1, a factor that has positive effects on matrix homeostasis by inhibiting the matrix metalloproteinases and whose expression is suppressed by IL-1. The combination of TGF-beta and the p38 MAPK inhibitor SB-203580 (an inhibitor of cartilage catabolism) showed the synergistic effect of inducing TIMP-1 expression in IL-1 activated chondrocytes to a level that was greater than the additive effects of both agents alone, and greater than that observed in the control cultures that were not treated with IL-1.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Increased levels of TIMP-1 should help restore the imbalance in matrix homeostasis that is the primary pathological feature of the osteoarthritic joint.

(2) Applicants submitted additional experimental data with the response filed on November 6, 2006, provided as the Moore Declaration, Exhibit G, evidencing the unexpected results and substantial benefits of the presently claimed invention. In particular, the Moore Declaration demonstrates that treating IL-1 stimulated chondrocytes with the combination of IL-1Ra and IGF-1 restored the ability of the chondrocytes to respond to IGF-1 and synthesize increased amounts of the two major cartilage matrix components, type II collagen and aggrecan, as shown in Exhibit G, FIGURES 2, 3, and 4. The Moore Declaration also demonstrates that a combination of IGF-1 and the NF-κB inhibitor inhibited the IL-1-induced aggrecanase activity to 43% of the maximal response, achieving substantially greater inhibition than either agent alone (Exhibit G, Figure 5.). The data presented in the Moore Declaration also demonstrates that for the concentrations of agents used, the combination of an anabolic agent (IGF-1) and either a p38 MAPK inhibitor (Exhibit G, Figure 8) or a NF-κB inhibitor (Exhibit G, Figure 9) is more effective than any of the respective single agents in suppressing the IL-1 induction of MMP-1 mRNA. By extension, treatment of an osteoarthritic joint with the combination of IGF-1 plus the tested p38 MAPK inhibitor or IGF-1 plus the tested NF-κB inhibitor should be more effective at inhibiting matrix degradation than treatment with any of these agents alone. In Example 4 of the Moore Declaration, it is shown that the combination of BMP-2 or BMP-7 and a p38 MAPK inhibitor would require ten-fold lower levels of the p38 inhibitor for maximal inhibition of proMMP-13 production by the chondrocytes in an osteoarthritic joint demonstrates the superiority of the combination compared to either agent alone. The local delivery of such combinations in accordance with the claimed methods of the present invention further reduce the potential for toxic side effects.

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Taken together, the foregoing evidence set forth in the previously submitted non-prior art references (Studer et al.) and in the declaration of Dr. Moore (Exhibit G) verifies that the present invention provides a disproportional increase in efficacy in combination relative to the efficacy of individual agents, as asserted in the specification, is commensurate in scope with the pending claims, and therefore clearly supports the patentability of the claims, as amended. Moreover, the experimental data described above demonstrates the surprising and remarkable effect that the evaluated inhibitors of cartilage catabolism, when administered together with an anabolic chondroprotective agent, have the potential to not only inhibit inflammation and matrix degradation, but to also restore the ability of the diseased chondrocytes to respond to the evaluated anabolic growth factors.

Thus, without the benefit of the applicants' disclosure, one of skill in the art would not be motivated by the teachings of the cited references, or by general knowledge in the art, to arrive at the claimed invention, and would have no reasonable expectation of success in practicing the invention as claimed. Accordingly, because the cited references teach directly away from the claimed invention, and because the general knowledge of one skilled in the art would not provide any basis or motivation to arrive at the claimed invention, Claims 38, 39, 44-51, 53, 73-76, and 81 are believed to be clearly patentable under 35 U.S.C. § 103(a) over U.S. Patent No. 5,972,880 (Pelletier et al.) in view of U.S. Patent No. 5,206,023 (Hunziker). Removal of this ground of rejection is respectfully requested.

New Claims

New Claims 82 and 83 have been added. Claim 82 depends from Claim 38 and is supported by the specification as filed, for example at page 13, line 31, to page 14, line 10; page 32, line 1, to page 69, line 32; and page 82, line 1, to page 83, line 29.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

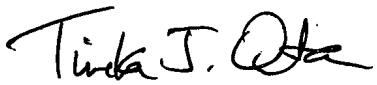
Claim 83 depends from Claim 73, and is supported by the specification as filed, for example at page 13, line 31, to page 14, line 10; page 32, line 1, to page 69, line 32; and page 82, line 1, to page 83, line 29.

CONCLUSION

In view of the foregoing remarks, applicants respectfully submit that all of the pending claims are in condition for allowance. Reconsideration and favorable action is requested. The Examiner is further requested to contact the applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]



Tineka J. Quinton
Registration No. 53,496
Direct Dial No. 206.695.1655

TJQ:jlg

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100